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NATIONAL INSTITUTES OF HEALTH
CONSENSUS DEVELOPMENT CONFERENCE STATEMENT
Hydroxyurea Treatment for Sickle Cell Disease
February 25–27, 2008

NIH consensus and state-of-the-science statements are prepared by independent panels of health professionals and public representatives on the basis of (1) the results of a systematic literature review prepared under contract with the Agency for Healthcare Research and Quality (AHRQ), (2) presentations by investigators working in areas relevant to the conference questions during a 2-day public session, (3) questions and statements from conference attendees during open discussion periods that are part of the public session, and (4) closed deliberations by the panel during the remainder of the second day and morning of the third. This statement is an independent report of the panel and is not a policy statement of the NIH or the Federal Government.

The statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

Introduction

Sickle cell disease is an inherited blood disorder that affects between 50,000 and 100,000 people in the United States. It is estimated that 2,000 babies are born with sickle cell disease in the United States each year. It was the first disease for which a specific molecular defect in a gene was identified. Sickle cell disease is the most common genetic disease identified as part of the Newborn Screening Program in the United States. The condition is chronic and lifelong, and it is associated with a decreased lifespan. Sickle cell disease is most common in people whose families come from Africa, South or Central America (especially Panama), Caribbean islands, Mediterranean countries (such as Turkey, Greece, and Italy), India, and Saudi Arabia.

Sickle cell disease occurs when an infant inherits the gene for sickle hemoglobin from both parents (Hb SS, or sickle cell anemia) or the gene for sickle hemoglobin from one parent and another abnormal hemoglobin gene from the other parent. In addition, approximately 2 million Americans have sickle cell trait (in which an infant inherits the gene for sickle hemoglobin from one parent and a normal hemoglobin gene from the other parent). There are several additional sickle syndromes as a result of genotypes which include, but are not limited to: SCD-Sβ^0, SCD-SC, SCD-SD, SCD-Sβ^+, and SCD-SO$_{arab}$.

The red blood cells in people who have sickle cell disease become deoxygenated (or depleted of oxygen), dehydrated, and crescent-shaped or "sickled." The cells aggregate, or clump

together, and stick to blood vessel walls. Aggregation blocks blood flow within limbs and organs. This can cause painful episodes and permanent damage to the eyes, brain, heart, lungs, kidneys, liver, bones, and spleen. Infections and lung disease are leading causes of death in people who have sickle cell disease.

Patients who have sickle cell disease are frequently seen in emergency departments and hospitalized for pain crises. Standard treatments for acute pain crises include painkilling medications, hydration, and oxygen.

The chemical hydroxyurea was initially synthesized in Germany in 1869. Nearly 50 years ago, it was developed as an anticancer drug. It has been used to treat myeloproliferative syndromes, some leukemias, melanoma, and ovarian cancer. It also has been used to treat psoriasis. The drug hydroxyurea was first tested on sickle cell disease in 1984. Initial studies show that it acts to increase the production of fetal hemoglobin-containing red blood cells and these dilute the number of sickled cells in circulation.

In the mid-1990s, a major study was conducted that randomized nearly 300 adult sickle cell patients who had more than three painful crises per year to hydroxyurea or placebo (an inactive pill). In the past, the term "pain crises" has been used. Currently, the term "severe pain episodes" is used. This study was stopped early, as it clearly showed that hydroxyurea reduced the number and severity of pain crises in sickle cell patients when compared to patients taking placebo. Follow-up with the trial participants, including patients who were originally given placebo and were later prescribed hydroxyurea after the drug was determined to be beneficial, has shown that hydroxyurea reduces the damaging effects of sickle cell disease and improves some aspects of quality of life. The drug also may extend survival. In 1998, the U.S. Food and Drug Administration approved hydroxyurea for prevention of pain crises in adults who have sickle cell anemia. Although the efficacy of hydroxyurea has been established in adults, the evidence of its efficacy in children is not as strong; however, the emerging data are supportive.

Although hydroxyurea is beneficial to some patients who have sickle cell disease, a number of unresolved issues about the use of the drug exist. These include a lack of providers devoted to treating sickle cell disease, as well as patient and health practitioner concerns about the overall safety and effectiveness of the drug.

To take a closer look at this important topic, the National Heart, Lung, and Blood Institute and the Office of Medical Applications of Research of the National Institutes of Health convened a Consensus Development Conference from February 25 to 27, 2008, to assess the available scientific evidence related to the following questions:

- What is the efficacy (results from clinical studies) of hydroxyurea treatment for patients who have sickle cell disease in three groups: infants, preadolescents, and adolescents/adults?

- What is the effectiveness (in everyday practice) of hydroxyurea treatment for patients who have sickle cell disease?

- What are the short- and long-term harms of hydroxyurea treatment?

- What are the barriers to hydroxyurea treatment for patients who have sickle cell disease, and what are the potential solutions?

- What are the future research needs?

1. What is the efficacy (results from clinical studies) of hydroxyurea treatment for patients who have sickle cell disease in three groups: infants, preadolescents, and adolescents/adults?

Efficacy refers to the therapeutic effect of an intervention in a controlled setting. This is in contrast to effectiveness, which is the therapeutic effect of an intervention in real-world situations. This section reviews the efficacy of hydroxyurea in the treatment of adults/adolescents, preadolescents, and infants who have sickle cell disease.

In this document, sickle cell disease refers to people who have the following genotypes: SCD-SS, SCD-Sβ^0, SCD-SC, SCD-SD, SCD-Sβ^+, and SCD-SO_{arab}. Efficacy studies have varied in their inclusion of specific genotypes but almost exclusively include SCD-SS. In addition, the geographic origin of sickle cell disease is associated with different haplotypes and varying degrees of clinical severity. The three most common haplotypes are Senegalese, Benin, and Bantu, and they are phenotypically different. Other geographic areas of origin associated with sickle cell disease include Saudi Arabia and the Indian subcontinent. Benin and Bantu haplotypes are more common among people residing in the Western Hemisphere and are associated with worse clinical outcomes. There may be implications for variable response to hydroxyurea therapy based on haplotype and/or genotype. Few attempts to assess efficacy have appropriately accounted for the heterogeneity of study populations who differed by genotype and phenotype. Also, few studies reported results for subgroups defined by demographic factors (e.g., sex and age group).

Although clinical experience on the use of hydroxyurea for treating sickle cell disease has been amassed over nearly 25 years, the strength of evidence supporting the efficacious use of hydroxyurea is not equivalent across age groups. Hydroxyurea is currently Food and Drug Administration-approved for use in adults and is the only treatment for sickle cell disease that modifies the disease process. The strength of evidence does vary greatly across the various age groups. Evidence is stronger in adults but more limited for children because of a weaker study design, small numbers of participants, and limited length of follow-up in the one available randomized clinical trial. Nonetheless, the evidence in children does not contradict the findings in adults that hydroxyurea improves hematological parameters and decreases hospitalization rates. Published evidence using weaker, observational study designs such as cohort studies, pre/poststudies, case series, and case reports does suggest that, overall, hydroxyurea is efficacious. Adding to the difficulty in reaching a consensus on the use of hydroxyurea is that published efficacy studies are difficult to interpret due to the use of a variety of outcome measures such as hematological endpoints; reduced incidence of pain crises, acute chest syndrome, hospitalizations, strokes, and kidney and spleen damage; as well as the need for transfusion therapy. The results of studies currently under way should provide more information regarding the benefit of hydroxyurea in prevention of organ damage and additional sickle cell

disease outcomes. Also, learning more about how the drug works is important in developing new drugs.

Adolescents/Adults

Strong evidence supports the efficacy of hydroxyurea use in adults. The published clinical trials included adolescents; however, they were not analyzed or reported as a separate group. There is a variety of outcomes, including blood markers as measures of treatment effect (e.g., hemoglobin level, hemoglobin F cells, percent hemoglobin F, mean corpuscular volume, white blood cells, and platelets). Studies have used a variety of clinical outcome measures (pain crises, hospitalizations, acute chest syndrome, blood transfusion therapy, mortality, priapism (unwanted prolonged painful erection), strokes, and leg ulcers). In addition, some studies have looked at effects of hydroxyurea on the spleen, kidneys, and blood flow to the brain. A summary of the outcomes evaluated in the adult studies is tabulated below.

Table 1. Summary of Study Outcomes for Adults Receiving Hydroxyurea for Sickle Cell Disease

Outcomes	Impact
Blood Markers	
Hemoglobin	↑↑↑
Percent fetal hemoglobin	↑↑↑
Mean corpuscular volume	↑↑↑
White blood cell count	↓↓↓
Clinical Outcomes	
Pain crises	↓↓↓
Hospitalizations	↓↓↓
Blood transfusion therapy	↓↓↓
Acute chest syndrome	↓↓↓
Priapism (painful erection)	←→ (not evaluated)
Strokes	←→ (not evaluated)
Leg ulcers	←→ (not significantly different)
Sepsis	←→ (not evaluated)
Prevention of End Organ Damage	
Spleen	←→ (not evaluated)
Kidney	←→ (not evaluated)
Brain (cerebral blood flow)	←→ (being evaluated)
Mortality	↓

↓↓↓ = high-grade evidence for a decrease; ↓ = low-grade evidence for a decrease; ↑↑↑ = high-grade evidence for an increase; ←→ = not significantly different or not evaluated or insufficient data.

Although a mortality reduction has been reported, the published trial was not specifically designed to assess this endpoint. It is therefore difficult to draw definitive conclusions about the impact of hydroxyurea on mortality.

Preadolescents

The evidence varies on whether the use of hydroxyurea improves short-term endpoints, especially hematological measures, in the preadolescent populations beyond infancy. A summary of study outcomes for preadolescents is shown in table 2.

Table 2. Summary of Study Outcomes for Preadolescent Children Beyond Infancy Receiving Hydroxyurea for Sickle Cell Disease

Outcomes	Impact
Blood Markers	
Hemoglobin	←→ (not significantly different)
Percent fetal hemoglobin	↑↑↑
Mean corpuscular volume	↑↑↑
White blood cell count	↓↓↓
Clinical Outcomes	
Pain crises	↓↓
Hospitalizations	↓↓↓
Blood transfusion therapy	←→ (insufficient data)
Acute chest syndrome	←→ (insufficient data)
Priapism (unwanted prolonged painful erection)	←→ (not evaluated)
Strokes	↓
Leg ulcers	←→ (not evaluated)
Sepsis	←→ (not evaluated)
Prevention of End Organ Damage	
Spleen	←→ (being evaluated)
Kidney	←→ (being evaluated)
Brain (cerebral blood flow)	←→ (being evaluated)
Mortality	←→ (insufficient data)

↓↓↓ = high-grade evidence for a decrease; ↓↓ = moderate-grade evidence for a decrease; ↓ = low-grade evidence for a decrease; ↑↑↑ = high-grade evidence for an increase; ←→ = not evaluated or not significantly different or insufficient data

There is strong evidence for an improvement in blood markers and reduced hospitalizations, and moderate evidence for a reduction in the incidence of pain crises. Ongoing investigations in this age group will determine the efficacy of hydroxyurea treatment for children who have SCD-SS, a history of strokes, and too much iron (iron overload).

Infants

At present, there are no published, well-designed clinical trials evaluating hydroxyurea treatment for infants. There are ongoing trials and observational studies assessing the efficacy of hydroxyurea in the treatment of infants who have sickle cell disease. The endpoints of these studies include prevention of damage to the kidney and spleen and improvements in blood markers that predict long-term clinical outcomes.

In summary, the efficacy of hydroxyurea treatment for adults who have SCD-SS is established. Although the evidence for efficacy of hydroxyurea treatment for children is not as strong, the emerging data are supportive. Future directions include evaluation of efficacy in preadolescent children and infants and further development of modalities of therapy, including stem cell transplant and gene therapy. Stem cell transplant can be curative in this disease.

2. What is the effectiveness (in everyday practice) of hydroxyurea treatment for patients who have sickle cell disease?

Effectiveness is defined as the therapeutic effect of an intervention as demonstrated or observed in patients in their usual care setting. The efficacy of hydroxyurea in sickle cell disease has been established. Although there are limited data regarding hydroxyurea's effectiveness, the experience of multiple physicians and clinics strongly suggests that the drug can be highly effective in widespread practice. One problem in determining the effectiveness of hydroxyurea treatment is the lack of a precise estimate of the number of people who have sickle cell disease in the United States and the lack of a precise estimate of the number of people actually receiving hydroxyurea treatment. Adherence is also affected by the fact that it often takes 3 to 6 months of treatment for the patient to have a clinical response. Another problem is that effectiveness is significantly impacted by adherence. Reasons for nonadherence are not fully understood.

It appears that most people who have received hydroxyurea have been treated in specialty clinics. Only a fraction of patients who might benefit from hydroxyurea have received treatment. Potentially, many more patients could benefit from treatment, including patients who have been excluded from research studies in the past. Studies have excluded patients who:

- Are pregnant
- Have substance abuse problems
- Have prior hydroxyurea therapy
- Have HIV infection
- Have had strokes within the past 6 years
- Have chronic opioid use

Some of the sickest sickle cell anemia patients have been excluded from studies. A much broader range of patients might benefit. For example, patients who have persistent sickle cell disease-induced pain require chronic opioid use.

Observational studies in both adults and children support the use of hydroxyurea in reducing the complications of sickle cell disease (including pain, hospitalizations, blood transfusions, and acute chest syndrome) and decreasing mortality. Although data are limited regarding effectiveness of hydroxyurea treatment for sickle cell disease, it does appear to be effective but is currently underutilized.

3. What are the short- and long-term harms of hydroxyurea treatment?

There are potential short-term and long-term effects of hydroxyurea treatment. The precise mechanisms by which hydroxyurea produces its varied effects are not known. However, a major mechanism is believed to be interference with an enzyme, ribonucleotide reductase, that is essential for DNA synthesis. Hydroxyurea's known and potential side effects appear to be related to its interference with rapidly dividing cells, particularly newly formed blood cells. We have defined short-term, or acute, effects as those conditions generally occurring within 6 months of hydroxyurea initiation; long-term effects are defined as conditions that are chronic and/or have an onset of greater than 6 months after initiation of hydroxyurea.

Short-Term Effects

The blood-related, short-term effects of hydroxyurea are dose-related and can be predicted based on its mechanism. These are intrinsic to the therapeutic effect of hydroxyurea. They include:

- A decrease in white blood cell count (leukopenia)
- A decrease in platelet count (thrombocytopenia)
- Decreased red blood cell count (anemia)
- Decreased reticulocytes (newly formed red blood cells)

A decrease in white blood cell count may predispose the patient to infection, and a decrease in platelets may predispose the patient to bleeding, so these blood cells are monitored regularly during therapy. Hydroxyurea's effect on blood is temporary and reversible. If white blood cell or platelet counts are too low, the dose of hydroxyurea is reduced or the hydroxyurea is discontinued. Careful monitoring of blood-related laboratory tests and dose adherence will usually prevent these side effects.

Another short-term effect among men taking hydroxyurea may be decreased sperm production, which may be temporary and reversible. Data are limited. There are no large studies of sperm production among men taking hydroxyurea for sickle cell disease. We are not aware of any reports of an increase in birth defects among the offspring of men who take hydroxyurea.

Hydroxyurea appears to cause dryness of the skin and darkening of the skin and nails, or hyperpigmentation (which also may be a long-term side effect).

Leg ulcers are common in adults who have sickle cell disease. In a randomized clinical trial comparing hydroxyurea and placebo, hydroxyurea did not appear to affect the development of leg ulcers in people who have sickle cell disease. Also, gastrointestinal tract symptoms were no more common among people who were taking hydroxyurea for sickle cell disease than among those who were not taking hydroxyurea.

Long-Term Effects

The potential long-term effects of hydroxyurea are birth defects in the offspring of people taking the drug, growth delays in children taking the drug, and malignancies in both children and adults who have taken the drug. These long-term harms may be permanent and irreversible, but they are not yet proven.

There have been concerns about hydroxyurea's potential to cause birth defects in humans, because it can cause birth defects in experimental animals. Pregnant rats and mice given hydroxyurea in very high doses have an increased number of offspring with birth defects. There does not, however, appear to be an increase in the number of birth defects among the offspring of women who have taken hydroxyurea during pregnancy. The long-term effects of hydroxyurea on children exposed to the drug in utero are unknown. Nonetheless, because of concerns about hydroxyurea's potential to cause birth defects, the drug is generally not prescribed to pregnant women. Men and women who are taking hydroxyurea are advised to use contraception. Women who are trying to become pregnant or become pregnant while taking hydroxyurea should stop taking the drug.

Children aged 5 to 15 who have sickle cell disease and are treated with hydroxyurea show growth rates similar to peers with sickle cell disease who are not on hydroxyurea.

Hydroxyurea has an excellent and longstanding safety profile in the treatment of myeloproliferative disorders, although cases of leukemia and other malignancies also have been reported in patients who have taken hydroxyurea for other blood conditions. Most of these conditions are blood disorders, such as polycythemia vera or essential thrombocytosis, and these conditions can progress spontaneously to leukemia. This makes it difficult to determine whether hydroxyurea itself causes leukemia. Cases of leukemia and other malignancies also have been reported among both children and adults who have taken hydroxyurea for the treatment of sickle cell disease. These cases are rare and appear to be no more common than among the general population. The risk of cancer appears to be no different for people who have sickle cell disease who have taken hydroxyurea than for those who have not.

Because both patients and providers have identified side effects as a concern that limits the use of hydroxyurea, more information on the incidence and severity of these side effects is essential for both patients and providers to make informed choices. These data could come from a registry of sickle cell disease patients. Nevertheless, the data currently available are reassuring with respect to the risks of both the short- and long-term harms of hydroxyurea.

The natural history of sickle cell disease results in frequent, painful crises and permanent damage to the eyes, brain, heart, lungs, kidneys, liver, bones, and spleen. Hydroxyurea reduces the frequency and severity of painful crises. The risks of hydroxyurea are acceptable compared to the risks of untreated sickle cell disease.

Table 3. Short- and Long-Term Side Effects of Hydroxyurea Treatment in People Who Have Sickle Cell Disease

Short-Term Side Effects	
Decreased white blood cell count (leukopenia) Decreased platelet count (thrombocytopenia) Decreased red blood cell count (anemia) (These side effects typically can be anticipated and prevented by temporary discontinuation of hydroxyurea or decrease in hydroxyurea dose. These side effects usually resolve within 1 to 2 weeks.)	Frequent, expected, and dose-related
Nausea (usually mild)* Skin rash Pneumonitis (lung inflammation)	Infrequent
Temporarily decreased sperm counts or sperm abnormalities*	Not adequately evaluated
Long-Term Side Effects	
Increased risk of superficial skin cancers* Skin and nail darkening (hyperpigmentation)	Infrequent
Permanently decreased sperm counts*	Not adequately evaluated
Reproductive Side Effects*	
When taken during pregnancy, hydroxyurea can theoretically increase the risk of miscarriage, birth defects, restricted fetal growth, or postnatal development. Sexually active couples should avoid pregnancy if either is on hydroxyurea.	

* Evidence grade is either insufficient or low that this is actually associated with the use of hydroxyurea.

4. What are the barriers to hydroxyurea treatment for patients who have sickle cell disease, and what are the potential solutions?

Barriers to hydroxyurea treatment for patients who have sickle cell disease can arise at four levels—patient, parent/family/caregiver, provider, and system. A systematic evidence review of the barriers to hydroxyurea treatment found only three studies that specifically addressed this issue and none that tested interventions to overcome barriers to hydroxyurea. The first study found that providers of adult sickle cell patients were reluctant to prescribe hydroxyurea because of patient concerns about side effects and their own concerns about patient adherence, patient age, side effects and carcinogenic risk, lack of patient contraception, and the costs to patients. Two additional studies examined barriers in pediatric patients who have sickle cell disease. The first study found that patients and parents/families/caregivers chose hydroxyurea therapy over

chronic transfusion and stem cell transplantation after hearing nonbiased information about all three potential treatments. Perceived efficacy and safety of potential treatments were used most commonly by patients and parents/families/caregivers to decide treatment. In the second study, the researchers concluded that some parents were unwilling to accept the use of hydroxyurea in their children because of concerns about cancer and birth defects. The Panel agreed to the inclusion of evidence obtained from expert testimony and studies analyzing barriers to the delivery of quality health care to sickle cell disease. These studies examined potential barriers to hydroxyurea treatment, including the receipt of routine, scheduled care; the adherence to medications; and receipt of therapies including pain control and prescriptions.

Some of the social, economic, and cultural characteristics of patients who have sickle cell disease are important in reviewing both barriers and solutions to access to hydroxyurea. Patients who have sickle cell disease are poorer than the national average but are more often covered by Medicaid. They also may be immigrants who are unable to obtain insurance. The care of children and adults who have sickle cell disease and the barriers to their care must be viewed within the context of their families, communities, and the American healthcare system. The care of patients who have sickle cell disease needs to be longitudinal across the lifespan, and the difficulties in transitioning their care from pediatric to adult settings remain a challenge.

Patient Level

- Fears about cancer, birth defects, infertility, and the uncertainty of other potential long-term risks
- Concern that the non-Food and Drug Administration-approved status of hydroxyurea for children means that hydroxyurea is an experimental drug
- Lack of knowledge about hydroxyurea as a therapeutic option
- Lack of perception that hydroxyurea is currently the only therapy that directly modifies the disease process
- Lack of adherence to treatment regimen
- Need for frequent monitoring of hydroxyurea response

Parent/Family/Caregiver Level

- Fears about cancer, birth defects, infertility, and the uncertainty of long-term risks
- Concern that the non-Food and Drug Administration-approved status of hydroxyurea for children means that hydroxyurea is an experimental drug
- Lack of knowledge about hydroxyurea as a therapeutic option

- Lack of perception that hydroxyurea is currently the only therapy that directly modifies the disease process

- Difficulty in communication between patients and their caregivers regarding the use of hydroxyurea and other therapeutic options

Provider Level

- Lack of knowledge about hydroxyurea as a therapeutic option

- Concerns about cancer, infertility, birth defects, and the uncertainty of long-term risks

- Provider bias and negative attitudes toward patients who have sickle cell disease and their treatment

- Lack of clarity in hydroxyurea treatment regimens and undertreatment in adults

- Limited number of physicians who have expertise in the use of hydroxyurea for sickle cell disease

- Failure to engage patients/caregivers in treatment decisionmaking in a developmentally appropriate manner

- Lack of perception that hydroxyurea is currently the only therapy that directly modifies the disease process

System Level

- Financing (lack of insurance, type of insurance, underinsurance, scope of coverage, copays, reimbursement, payment structures)

- Geographic isolation

- Lack of coordination between academic centers and community-based clinicians

- Limited access to comprehensive care centers and comprehensive care models

- Problems in transitioning from pediatric to adult care

- Limited access (e.g., geographic distribution, recruitment, and retention of clinicians competent in the provision of comprehensive care to patients who have sickle cell disease)

- Inadequate Government, industry, and philanthropic support for the care of patients who have sickle cell disease

- Development and promotion of hydroxyurea are hindered by lack of commercial interest in the development and promotion of hydroxyurea

- Lack of visibility and empowerment of sickle cell disease advocacy groups

- Cultural and language barriers to the provision of appropriate care

- Inadequate information technology systems to support the long-term care of patients who have sickle cell disease

Solutions

- Promote models of care (e.g., comprehensive care, medical home, family-centered) across the lifespan that support quality of care and improved access to evidence-based treatment, including hydroxyurea.

- Provide multidisciplinary care (e.g., health educators, social workers, case managers, physicians, and nurses) to improve the physical and mental health of patients who have sickle cell disease and the financing structures to support such care.

- Provide support for community health worker models (e.g., patient navigators, patient advocates, and peer advocates).

- Provide support for coordination and comanagement of patients with the use of telemedicine.

- Ensure better translation of findings to the patient and caregiver populations using culturally or language-appropriate written and visual materials.

- Implement health promotion models in educational interventions for adherence to therapies.

- Engage and support community-based efforts to improve knowledge of the benefits and risks of hydroxyurea.

- Improve Federal, State, and local coordination of activities regarding sickle cell disease.

- Provide support for cultural competency training across the interdisciplinary team regarding care for sickle cell disease.

- Improve insurance coverage of sickle cell disease (e.g., extend Medicare coverage to adult sickle cell disease patients, or extend the age qualifications of Medicaid).

- Eliminate barriers that restrict access to public insurance.

- Support ongoing training of health professionals to achieve and maintain competence in the care of patients who have sickle cell disease, including hydroxyurea treatment.

- Increase funding by Government, industry, and philanthropic organizations for patients who have sickle cell disease.

- Encourage partnership and support of advocacy groups for sickle cell disease.

- Develop enhanced information systems to better coordinate delivery of care in the healthcare system.

5. What are the future research needs?

There is a need for a surveillance system of patients who have sickle cell disease that will be followed prospectively. This system should contain demographic, laboratory, clinical, treatment, and outcome information.

Based on the information presented in answers to questions 1 through 4, we support the utilization of hydroxyurea for the treatment of sickle cell disease but recognize that additional research is required to provide information that will ensure the most appropriate application of this modality.

Additional efficacy studies of hydroxyurea are required. These studies will evaluate the efficacy of hydroxyurea as measured in terms of clinical and laboratory outcomes:

- To define the mechanisms of action of hydroxyurea in a clinical setting

- To use pharmacokinetic and clinical measures to determine optimal dosing, dose titration, and clinical efficacy

- To identify the factors that predict clinical response and nonresponse to hydroxyurea

- To confirm the validity of hemoglobin as a surrogate for benefit

Additional effectiveness studies are required. These studies will examine the effectiveness of hydroxyurea as measured in terms of clinical and laboratory outcomes. These effectiveness studies should determine the population of patients who have sickle cell disease and who will benefit from hydroxyurea. This would include considerations of when to begin the use of hydroxyurea to treat or prevent complications of sickle cell disease and how long to continue its use. These studies should complement those that are currently in progress.

Although we believe hydroxyurea to be safe and effective, additional studies of the safety, clinical effectiveness, and cost-effectiveness of hydroxyurea are required. Appropriate studies need to be conducted to provide more information about:

- Developmental and reproductive adverse effects

- Carcinogenic risk

- Long-term clinical outcomes, including quality of life

- Evaluation of the utility and cost-effectiveness of the comprehensive care and medical home models for the delivery of hydroxyurea treatment

- Evaluation of the role of the case manager in delivery of hydroxyurea treatment

- Evaluation of interventions aimed at reducing parent/caregiver, provider, and healthcare system barriers to hydroxyurea treatment

Conclusions

The burden of suffering is tremendous among many patients who have sickle cell disease. These patients experience disease-related pain many days of their lives and usually do not seek medical attention until their symptoms are overwhelming. They often attempt to treat themselves and, thus, do not always come to the attention of the healthcare system. Obtaining optimal care is challenging for the patient who has sickle cell disease. Many patients are not in a coordinated program aimed at prevention of long-term complications and acute pain crises. They rely heavily on emergency and acute care facilities for pain control.

Obtaining specialty care can be a significant challenge as the number of health professionals trained to treat the disease is limited and the number of professionals specializing in the treatment of this disease is declining. The likelihood of patients who have sickle cell disease having a principal physician is low. There is a special challenge in transitioning from pediatric care to adult care. Many children rely on public insurance for their care. Gaps in coverage occur, leading to gaps in care.

No population-based registries exist that provide good estimates of the number of people who have this disease. Surveys do indicate that a large proportion of patients who have sickle cell disease are poor and from underserved communities. The overwhelming majority of patients who have sickle cell disease are ethnic minorities. For many, the limited resources and lack of culturally competent care by experienced clinicians set the stage for suboptimal care.

Hydroxyurea is an important major advance in the treatment of sickle cell disease.

- **What is the efficacy (results from clinical studies) of hydroxyurea treatment for patients who have sickle cell disease in three groups: infants, preadolescents, and adolescents/adults?**

  - Strong evidence is found in support of the efficacy of hydroxyurea use in adults (decrease in pain crises, hospitalizations, blood transfusions, and acute chest syndrome).

  - Variable evidence is available in the preadolescent population (decrease in hospitalizations and pain crises).

- No well-designed clinical trial evidence in infants is available.

- Although the evidence for efficacy of hydroxyurea treatment for children is not as strong, the emerging data are supportive.

- **What is the effectiveness (in everyday practice) of hydroxyurea treatment for patients who have sickle cell disease?**

  - One problem in determining effectiveness is the lack of a precise estimate of the number of people who have sickle cell disease in the United States and the number of people actually receiving hydroxyurea.

  - Most published studies have strict entry criteria, meaning some patients with comorbidities who might benefit have not been assessed.

  - Overall, data regarding effectiveness are very limited.

- **What are the short- and long-term harms of hydroxyurea treatment?**

  - Short-term, dose-related, usually temporary, and reversible effects may be:

    - Decrease in white blood cell count (increased risk for infections).

    - Decrease in platelet count (increased risk for bleeding).

    - Decreased sperm counts or increased sperm abnormalities in men.

    - Dryness and darkening of the skin and nails.

  - No high-quality evidence supports:

    - Increased incidence of cancer.

    - Increased incidence of birth defects (although contraception is advised for men and women taking hydroxyurea, and discontinuation of hydroxyurea with pregnancy is recommended).

  - Moderate evidence shows that hydroxyurea does not affect growth rate in patients who have sickle cell disease.

  - The data currently available are reassuring with respect to the risks of both short- and long-term harms of hydroxyurea treatment.

  - The risks of hydroxyurea in adults are acceptable compared to the risks of untreated sickle cell disease.

- **What are the barriers to hydroxyurea treatment for patients who have sickle cell disease, and what are the potential solutions?**
  - Four levels of barriers exist: patient, parent/family/caregiver, provider, and system.
  - Only three studies specifically address barriers, and none addresses hydroxyurea interventions.
  - Patient and parent/family/caregiver barriers include:
    - Fears about cancer, birth defects, infertility, and uncertainty of other potential long-term risks.
    - Lack of knowledge of hydroxyurea as a therapeutic option for sickle cell disease.
  - Provider barriers include:
    - Limited number of physicians who have expertise in the use of hydroxyurea for sickle cell disease.
    - Provider bias and negative attitudes toward patients who have sickle cell disease and their treatment.
    - Lack of clarity in hydroxyurea treatment regimens and undertreatment.
  - System barriers include:
    - Financing: lack of insurance and coverage.
    - Geographic isolation, limited access to comprehensive care models.
    - Problems in transitioning from pediatric to adult care.
- **What are the future research needs?**
  - A comprehensive registry of all patients who have sickle cell disease that will be followed prospectively
  - Studies to better define the mechanism of action of hydroxyurea, as well as optimal dosing, titration, and monitoring
  - Studies that identify factors that predict clinical hydroxyurea response/nonresponse
  - Effectiveness studies considering when to begin use of hydroxyurea to prevent or treat complications of sickle cell disease and how long to continue the therapy
  - Evaluation of the utility and cost-effectiveness of the comprehensive care and medical home models for the delivery of hydroxyurea treatment

The best way to achieve optimal care for patients who have sickle cell disease, including preventive care, is for the patients to be treated in clinics specializing in the care of this disease. All sickle cell patients should have a principal healthcare provider, and that provider, if not a hematologist, should be in frequent consultation with one. The National Institutes of Health funds sickle cell research centers, and several States currently support sickle cell specialty clinics. There is a critical need for increased funding for basic, clinical, and social research on this disease. There is an urgent need to organize and network centers specializing in the treatment of this disease.

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